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13. ABSTRACT *(Maximum 200 words)*

Six Phase I clinical pharmacology studies were performed during this contract period under the Task Order numbers 90-01, 92-04, 92-05, 94-06, 94-07 and 94-09. Task Order 90-01 produced data suggesting that the Mark I auto-injector produced effective and desirable blood levels and effects of atropine and 2-PAM compared to other prototype auto-injectors. Task Order 92-04 demonstrated that WR 238, 605 was safe and well tolerated at single doses up to 600 mg. Task Order 92-05 compared the blood levels produced by a new dosing regimen for halofantrine in the fed compared to the fasting state. Task Order 94-06 demonstrated the lack of irritating potential for a topical skin protectant. Task Order 94-07 demonstrated the safety of weekly dosing with the antimalarial WR 238, 605 and documented the accumulation of non toxic methemoglobin levels at the higher doses. This side effect may be beneficial in prophylaxis against cyanide poisoning. Task Order 94-09 showed a lack of toxicity from multiple dose pyridostigmine bromide in healthy male and female subjects of different weights.

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Kenneth C Carter 8/15/97

PI - Signature Date

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Introduction

This final report describes the activities conducted by South Florida Drug Research Corporation under task orders issued by the U.S. Army Medical Research and Materiel Command during the period of April 1, 1990 through September 30, 1997, which is the entire duration of Contract No. DAMD17-90-C-0042. South Florida Drug Research Corporation is an independent organization which has been conducting phase I clinical pharmacology studies for various sponsors since 1977. Their clinical pharmacology research unit is located at 2060 N.W. 22nd Avenue, Miami, Florida. This is a 72 bed research facility which is well equipped and staffed to conduct the types of studies conducted under this contract. Over the duration of this contract the effort expended by South Florida Drug Research Corporation on task orders issued by the U.S. Army Medical Research and Materiel Command accounted for approximately 10% of their total effort with the other 90% devoted to commercial phase I clinical pharmacology studies.

All studies described herein were performed according to written protocols which were developed by South Florida Drug Research Corporation in consultation with personnel from the U.S. Army Medical Research and Materiel Command. Before any human subject participated in these research studies, the Study Protocol and a written Informed Consent Form were presented to and approved by the First Foundation for the Protection of Human Subjects in Research (a properly constituted local Institutional Review Board) as well as the Human Subjects Research Review Board of the U.S. Army. The data for each individual subject was collected and reported in individual case report forms which were designed by South Florida Drug Research Corporation. These completed case report forms have been examined by U. S. Army personnel and verified against the original source documents in the subject's charts. This is the source of the data then utilized to prepare the final study reports that were submitted for each study. These case report forms are maintained by South Florida Drug Research Corporation until such time as they can be destroyed according to regulations in effect at that time.

Body of Report

During the period of the contract South Florida Drug Research Corporation worked on the following task orders:

1. Task Order 90-01

Title: "A Three Way Crossover Study of Atropine and 2-PAM Absorption: A Comparison of the Mark I with Multi-chambered Auto-injectors."

The clinical portion of this study was conducted during the period from October 21st, 1990 through November 11th, 1990. This study compared the pharmacokinetics and pharmacodynamics of atropine and 2-PAM from three auto-injector devices: two with multiple chambers delivering atropine and 2-PAM into one intramuscular site (the STI prototype and Duphar prototype) and the third delivering the two drugs into two separate sites (the Mark I device). Comparison of the three devices was based on four separate physiological endpoints of atropine action (heart rate, salivary secretion, pupil size and near point of visual accommodation) and also on serum levels achieved for atropine and 2-PAM. The results of this study are the subject of a final report issued in August, 1991 which concluded that the study suggested that the overall pharmacokinetic and pharmacodynamic profile produced by the Mark I device was potentially more desirable than that produced by the other prototypes.

2. Task Order 92-04

Title: "Rising, Single Oral Dose Safety and Tolerance Study of WR 238,605."

The clinical portion of this study was conducted during the period between July 1992 and January 1994. As the title implies, this study probed the safety and tolerance of this new antimalarial compound in cohorts of 5 normal healthy males (three active, two placebo) from doses of 4 mg (base) through 600 mg (base). It was concluded from this study that WR 238,605 was well tolerated in single doses up to and including 600 mg. This study was felt to support the initiation of studies to investigate multiple dosing with this compound. Special attention was focused on methemoglobin values because of the biochemical mechanism of this drug. Although methemoglobin values above normal were observed at the highest doses, none of these findings were felt to be limiting. The clinical results of this study are the subject of a final report issued in February 1996. The pharmacokinetic results were the subject of a separate report prepared by the U.S. Army personnel.

3. Task Order 92-05

Title: "Pharmacokinetics of a New Multiple Dose Halofantrine Regimen."

The clinical portion of this study was conducted during the period between February 7th , 1993 and April 12th , 1993. This study was designed to evaluate the blood levels produced by a new proposed dosage regimen which was thought to be more likely to be successful in treatment of cases of multi-drug resistant cases of malaria. This regimen was also studied in two dietary states (fasting and immediately following a fatty meal). Since one of the known toxic side effects of high halofantrine blood levels was prolongation of the QT_c interval , frequent electrocardiograms were obtained as a safety precaution. The results of this study indicated that the halofantrine regimen employing 500 mg every 6 hours for three doses and then 500 mg every 24 hours for 6 days, was well tolerated in healthy male subjects in either the fasting or fed state. Both pharmacokinetic measurements and ECG findings indicated that higher halofantrine levels were achieved in the fed state. These results are presented in the Final Study Report dated June, 1994, prepared by the Investigator and in a Pharmacokinetic report prepared by the U. S. Army. Further studies were suggested to determine if this regimen will be safe in older and non-healthy patients who may already have a propensity to develop cardiac arrhythmias

4. Task Order 94-06

Title: " Protocol No. 1: An assessment of the Irritancy Potential of a Candidate Topical Skin Protectant (TSP)."

" Protocol No. 2: An Assessment of the Contact Sensitization and Contact Photo Allergic Potentials of a Topical Skin Protectant (TSP)."

As the title implies, this task order required the preparation and execution of two separate clinical protocols. Protocol No. 1 was performed during the period from March 13th, 1995 until April 1st, 1995. Protocol No. 2 was performed during the period from April 3rd, 1995 until May 21st, 1995. The results of Protocol No. 1 were contained in the final clinical report dated November 9th, 1995 and concluded that this formulation of TSP cream did not cause contact dermal irritation either with of without ultraviolet irradiation and was safe under the experimental conditions of the test. The results of Protocol No. 2 were contained in the final clinical report dated February 14th, 1996 and concluded that this formulation of TSP cream was safe and well tolerated by healthy normal subjects both on a contact sensitization basis and under photo stimulated conditions.

5. Task Order 94-07

Title: " A Multiple Dose Safety, Tolerance and Pharmacokinetic Study of WR 238,605."

The clinical portion of this study was conducted during the period from April 20th, 1995 until November 29th, 1995. Three groups of twelve subjects each received weekly doses of WR 238,605 or placebo (8 active, 4 placebo) for ten weeks, in a fasting state. The

enrollment was staggered such that the lowest dose group (250 mg) was thought to have achieved steady state before dosing with the intermediate dose group (500 mg) was begun and that group was thought to have achieved steady state before the highest dose group was dosed. There was a ten week follow-up period with clinic visits every two weeks. The results of this study are contained in the final clinical report dated July 30th, 1997. The most striking result is the dose related accumulation of methemoglobin in these subjects. Even at the highest dose level, however, this was not a limiting toxicity. Indeed the subjects all tolerated the drug at these dose levels but there was a definite incidence of gastrointestinal side effects at the 750 mg dose and in some subjects at the 500 mg dose. The results certainly justify further investigation of the drug in the population that it is intended to treat.

6. Task Order 94-09

Title: "A Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Pyridostigmine when given in Single and Multiple Doses to Males and Females in Different Weight Groups."

The clinical portion of this study was conducted during the period from November 27th, 1994 until April 14th, 1995. A dose of pyridostigmine estimated to produce approximately a 20% inhibition of cholinesterase was administered to 6 different groups of normal healthy subjects (each containing 10 active and 5 placebo subjects). Three groups were male and three were female. Of the three they were stratified into low, medium and high weights to mimic the composition of the subjects who might receive these drugs under wartime conditions as prophylaxis against nerve gas poisoning. All subjects were dosed every 8 hours for 21 days and then received a single dose on day 22. Both the clinical and pharmacokinetic results are the subject of a final clinical/pharmacokinetic report issued on April 3rd, 1996. Essentially the results supported the previous use of this regimen and found no significant adverse experiences.

A one year outpatient follow-up of the 90 subjects listed above was also conducted. This was the subject of a clinical report dated August 1996 and finalized in March 1997. Only 4 of the 90 subjects did not complete any follow-up and indeed 330 of the scheduled 360 clinic visits were completed. Only four adverse experiences were identified: Two were uneventful pregnancies, one was a skin rash felt "possibly related" as a fixed drug eruption and the fourth was anemia related to overzealous donation of blood for remuneration. The one year follow-up failed to reveal any significant trend towards adversity in the subjects who received drug versus those who received placebo. Furthermore, there was no apparent difference between sexes and the different weight groups.

Conclusions

It is not possible to generalize about the conclusions in this type of contract since each Task Order really stands alone and develops its own conclusions which may or may not be related to the other Task Orders conducted under the contract. Essentially the conclusions from each Task Order are summarized in the sections above. The only other conclusion which has not been enumerated is that WR 238, 605, investigated above in Task Orders 92-04 and 94-07 appears to be a safe and effective methemoglobin generator. This pharmacologic property could be employed to create a resistance to cyanide poisoning and indeed there are future plans to investigate this possibility.

Bibliography of all Publications from this Effort

1. Brueckner, R., Coster, T., Wescher, D., Shmuklarsky, M., **Lasseter, K.C.** and Schuster, B. : Safety, Tolerance, Pharmacokinetics and Preliminary Antimalarial Efficacy of WR 238605 in Man. (Presented at the American Society of Tropical Medicine and Hygiene Meeting, 1995.)

2. Marino, M. T., Schuster, B.T., Brueckner, R.P., Clawson, R., Lin, E., Kaminskis, A. and Lasseter, K. C.: A Population Analysis of the Pharmacokinetics and Pharmacodynamics of Pyridostigmine Bromide in Man. J. Pharm. Pharm. Submitted for publication.

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